

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/06730

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C12Q1/68 G01N33/68 A61K38/46 A61K31/20 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C12Q A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| A | WO 95 24504 A (PASTEUR INSTITUT ;INST NAT SANTE RECH MED (FR); AMOUYEL PHILIPPE () 14 September 1995 (1995-09-14) cited in the application the whole document --- | 1-9 |
| A | KUO Y-M, ET AL.: "Elevated low-density lipoprotein in Alzheimer's Disease correlates with brain Abeta 1-42 levels" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 252, 1998, pages 711-715, XP002126049 the whole document --- | 1 -/- |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

9 February 2001

Date of mailing of the international search report

15/02/2001

Name and mailing address of the ISA
 European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Osborne, H

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/06730

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|--|------------------|
| WO 9524504 | A 14-09-1995 | FR 2716894 A | | 08-09-1995 |
| | | AT 169343 T | | 15-08-1998 |
| | | CA 2184635 A | | 14-09-1995 |
| | | DE 69503885 D | | 10-09-1998 |
| | | DE 69503885 T | | 22-04-1999 |
| | | DK 749498 T | | 10-05-1999 |
| | | EP 0749498 A | | 27-12-1996 |
| | | JP 9511138 T | | 11-11-1997 |
| | | US 5942392 A | | 24-08-1999 |
| ----- | | | | |
| WO 9818429 | A 07-05-1998 | US 5773432 A | | 30-06-1998 |
| | | AU 4948497 A | | 22-05-1998 |
| | | BR 9712580 A | | 07-12-1999 |
| | | CN 1235548 A | | 17-11-1999 |
| | | CZ 9901500 A | | 17-11-1999 |
| | | EP 0941096 A | | 15-09-1999 |
| | | HU 9904498 A | | 28-05-2000 |
| | | NO 992061 A | | 29-04-1999 |
| | | PL 332956 A | | 25-10-1999 |
| ----- | | | | |
| WO 9609392 | A 28-03-1996 | US 5599706 A | | 04-02-1997 |
| | | AU 3720295 A | | 09-04-1996 |
| | | CA 2199727 A | | 28-03-1996 |
| | | EP 0782622 A | | 09-07-1997 |
| | | JP 10506016 T | | 16-06-1998 |
| | | US 5877022 A | | 02-03-1999 |
| ----- | | | | |

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/06730

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | KURIYAMA M ET AL: "Low levels of apolipoprotein A1 and A11 in senile dementia" JAPANESE JOURNAL OF PSYCHIATRY AND NEUROLOGY, vol. 48, no. 3, - September 1994 (1994-09) pages 589-93, XP000863586 see abstract --- | 1 |
| A | WO 98 18429 A (SCHERING AG) 7 May 1998 (1998-05-07) the whole document --- | 10 |
| A | WO 96 09392 A (RIBOZYME PHARM INC) 28 March 1996 (1996-03-28) the whole document ----- | 10,12,13 |

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|---|--|
| Applicant's or agent's file reference BET 00/0648 | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/EP 00/06730 | International filing date (day/month/year) 07/07/2000 | (Earliest) Priority Date (day/month/year) 09/07/1999 |
| Applicant INSTITUT PASTEUR DE LILLE | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
 - contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished
- 2. **Certain claims were found unsearchable** (See Box I).
- 3. **Unity of invention is lacking** (see Box II).
- 4. With regard to the **title**,
 - the text is approved as submitted by the applicant.
 - the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

PATENT COOPERATION TREATY

PCT

REC'D 31 JUL 2001

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

| | | | |
|--|--|--|---|
| Applicant's or agent's file reference BET 00/0648 | FOR FURTHER ACTION | | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/EP00/06730 | International filing date (day/month/year) 07/07/2000 | Priority date (day/month/year) 09/07/1999 | |
| International Patent Classification (IPC) or national classification and IPC C12Q1/68 | | | |
| Applicant INSTITUT PASTEUR DE LILLE et al. | | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

| | |
|---|--|
| Date of submission of the demand 02/01/2001 | Date of completion of this report 25.07.2001 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Knudsen, H Telephone No. +49 89 2399 8696 |



INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

International application No. PCT/EP00/06730

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
Description, pages:

1-13 as originally filed

Claims, No.:

1-20 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/06730

the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c));
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

| | | | |
|-------------------------------|------|--------|------|
| Novelty (N) | Yes: | Claims | 1-20 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-20 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-20 |
| | No: | Claims | |

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

NOVELTY:

- 5.1 The closest prior art is disclosed in "KUO Y-M, ET AL.: 'Elevated low-density lipoprotein in Alzheimer's Disease correlates with brain A β 1-42 levels' BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 252, 1998, pages 711-715" (D1). This document discloses that the level of LDL is much higher in AD patients than in controls. Moreover, the $\epsilon 4$ allele is mentioned as a significant risk factor. However, D1 does not mention anything about Apo(a) or Lp(a) levels in $\epsilon 4$ positive and $\epsilon 4$ negative patients and the method of claim 1 is therefore novel over D1. None of the other cited prior art documents disclose that Apo(a) or Lp(a) are present in elevated levels in AD patients. Claims 1-9 are therefore novel.
- 5.2 The use of reagents which decrease the plasmatic level of Lp(a) or inhibits the binding of apoA/Lp(a) to its receptor in the treatment of AD in patients which carry an $\epsilon 4$ allele is not suggested either. Claims 10-20 are therefore considered novel.

INVENTIVE STEP:

- 5.3 The method of claims 1-9 differ from D1 in that ApoA/Lp(a) is used as a marker for AD. Given that none of the cited documents show a difference in the level of Apo(a)/Lp(a) between AD patients and controls and that the $\epsilon 4$ polymorphism is not in general linked to an elevated level of Apo(a)/Lp(a), this use of Apo(a)/Lp(a) is considered entirely unobvious and an inventive step therefore can be acknowledged for claims 1-9.
- 5.4 An inventive step is acknowledged for claims 10-20 as well. None of the cited prior art documents mention the possibility of treating Alzheimer's disease with medicaments which are capable of decreasing the plasmatic level of Apo(a) or Lp(a).

INDUSTRIAL APPLICABILITY:

- 5.6 Present claims 1-20 seem industrially applicable.

Re Item VII

Certain defects in the international application

- 7.1 Contrary to the requirements of Rule 5(a)(ii) PCT, the closest prior art documents D1 is not identified in the description and the relevant background art disclosed therein is not briefly discussed.

Re Item VIII

Certain observations on the international application

- 8.1 At present, the application only shows that the level of Lp(a) is increased in patients already suffering from AD according to clinical measures. However, the data are not sufficient to show that Lp(a) or ApoA can be used as a prognostic marker for AD. Claims 1-9 therefore lack support in the description.
- 8.2 The examples show that Lp(a) is measured with two antibodies binding to different epitopes of ApoA. It is for consideration whether Lp(a) or ApoA is determined accurately by this method.
- 8.3 In claim 5, the essential feature that the primers must be capable of amplifying the part of the APO E gene on which $\epsilon 4$ is situated has been omitted.
- 8.4 The definition of a compound in present claim 10 which states that the compound is capable of decreasing the level of Lp(a) places an undue burden on the skilled person wishing to know whether a certain medicament falls within the scope this claim. The reaction in human beings to medicaments is known to vary interindividually and the practitioner would therefore have to test every medicament on a large group of patients before knowing whether or not the use of the medicament falls within the scope of present claim 10. It therefore appears that present claim 10 is not sufficiently disclosed in the application.
- 8.5 The same objection applies mutatis mutandis to present claim 13 and is even reinforced by the fact that it is not clear how an inhibition of the production of ApoA/Lp(a) in the body can be measured.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/06730

8.6 The IPEA does not understand the intended meaning of the wording "and namely consists of ...". The claims should unambiguously show whether or not this wording has a limiting effect on the scope of the claims.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 January 2001 (18.01.2001)

PCT

(10) International Publication Number
WO 01/04349 A3

- (51) International Patent Classification⁷: **C12Q 1/68**,
G01N 33/68, A61K 38/46, 31/20, A61P 25/28
- (21) International Application Number: **PCT/EP00/06730**
- (22) International Filing Date: **7 July 2000 (07.07.2000)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:
99401742.4 **9 July 1999 (09.07.1999)** EP
- (71) Applicants (for all designated States except US): **INSTITUT PASTEUR DE LILLE [FR/FR]**; 1, rue du Professeur Calmette, F-59019 Lille Cedex (FR). **CENTRE HOSPITALIER UNIVERSITAIRE VAUDOIS DE LAUSANNE [CH/CH]**; Rue du Bugnon 9, CH-1011 Lausanne (CH). **INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM) [FR/FR]**; 101, rue de Tolbiac, F-75654 Paris Cedex 13 (FR).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **MOOSER, Vincent [CH/CH]**; 9, rue du Bugnon, CHUV, CH-1011 Lausanne (CH). **HELBECKQUE, Nicole [FR/FR]**; 10, rue Félix Faure, F-59750 Marcq En Baroeul (FR). **AMOUYEL**,
- Philippe [FR/FR]; 75, rue du Quesne, F-59700 Marcq en Baroeul (FR).
- (74) Agent: **JACOBSON, Claude**; Cabinet Lavoix, 2, place d'Estienne d'Orves, F-75441 Paris Cedex 09 (FR).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— *With international search report.*
- (88) Date of publication of the international search report:
25 May 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

A3

WO 01/04349

(54) Title: **METHOD FOR THE DIAGNOSIS OR THE PROGNOSIS OF ALZHEIMER DISEASE THERAPEUTICAL COMPOSITION FOR PREVENTING OR TREATING ALZHEIMER DISEASE**

(57) Abstract: The invention relates to a method of predicting an increased risk of a patient having Alzheimer's disease (AD) or for a subject of developing AD comprising: a) assaying a DNA-containing biological sample for the allele of the APOE gene; b) assaying the plasmatic level of protein Lp(a) or glycoprotein Apo(a), wherein the presence of an ε4 allele of the APOE gene and an increased plasmatic level of [Lp(a)]/Apo(a) indicates an increased risk for the patient having Alzheimer's disease or developing AD. The invention further provides a therapy for preventing or treating AD consisting of decreasing the plasmatic level of Lp(a) or the interaction of Lp(a) with its receptor in a patient bearing at least one APOE ε4 allele.